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Enantiospecific Synthesis of *ortho*-Substituted Benzylic Boronic Esters by a 1,2-Metalate Rearrangement/1,3-Borotropic Shift Sequence

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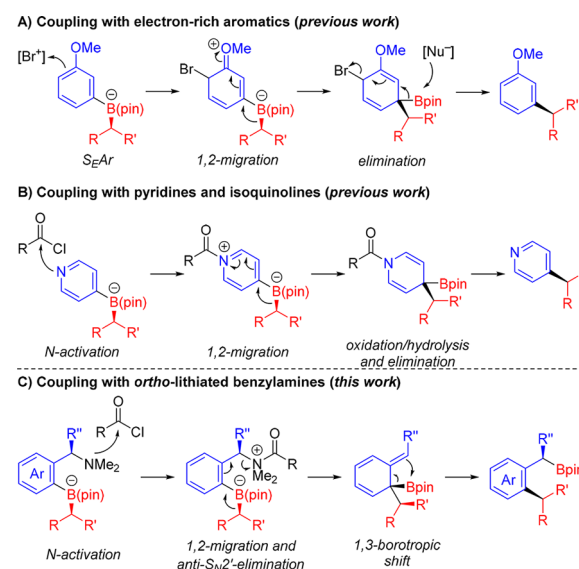
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S Supporting Information

ABSTRACT: Coupling reactions between benzylamines and boronic esters have been investigated. *ortho*-Lithiated benzylamines react with boronic esters and a *N*-activator to afford *ortho*-substituted benzylic boronic esters with formal 1,1'-benzylidene insertion into the C–B bond. The reaction occurs by a S_N2' elimination and 1,2-metalate rearrangement of the *N*-activated boronate complex to afford a dearomatized intermediate, which undergoes a Lewis-acid catalyzed 1,3-borotropic shift to afford the boronic ester products in high yield and with excellent enantiospecificity. The use of enantioenriched α -substituted benzylamines gave the corresponding secondary boronic esters with high ee.

The enantiospecific coupling of secondary and tertiary boronic esters to aromatics through transition-metal catalyzed processes is challenging.¹ Although some progress has been made enabling certain secondary boronic esters to be employed, the reactions are not generally applicable.^{2,3} We recently reported an alternative transition metal-free and stereospecific sp^2 – sp^3 coupling of chiral secondary and tertiary boronic esters with electron-rich aryl lithium reagents that showed considerable scope (Scheme 1a).⁴ In related work, we⁵ (and Ready⁶) showed that pyridines could also be coupled with complete stereospecificity to a similar range of boronic esters (Scheme 1b). These processes involve four basic steps: (i) boronate formation, (ii) activation, (iii) 1,2-migration, and (iv) elimination/rearomatization. We reasoned that this methodology would be significantly enhanced if the boron moiety could be retained in the product because of its broad versatility.⁷ Inspired by the coupling reactions with pyridines, we considered a related transformation with *ortho*-lithiated benzylamines (Scheme 1c).⁸ We considered that *N*-activation of the corresponding boronate complex would trigger the 1,2-migration/*anti*- S_N2' elimination of the carbamate to give a dearomatized intermediate, which should undergo a *suprafacial* 1,3-borotropic shift.⁹ This would lead to the desired aromatic product in which the boron moiety is retained. Although the 1,3-borotropic shift of allylic boronic acid pinacol esters is exceedingly slow,¹⁰ we reasoned that the driving force of aromatization would facilitate this rearrangement. In this communication, we describe the realization of this transformation to give a variety of *ortho*-substituted benzylic boronic esters in high yield and with excellent enantiospecificity.

Scheme 1. Enantiospecific sp^2 – sp^3 Couplings of Boronic Esters with Electron-Rich Aromatic (A) or Pyridines (B) and Proposed Work



We began our study by reacting (2-((dimethylamino)methyl)phenyl)lithium (**Li-1a**) with CyBpin (**2a**) to give the corresponding boronate complex and screened a broad range of *N*-activators (see SI for details). Among the electrophiles tested, $\text{ClCO}_2\text{CMe}_2\text{CCl}_3$ ($\text{Me}_2\text{Troc-Cl}$) was highly selective giving the dearomatized intermediate over boronic ester side products, rapidly, even at low temperature. However, despite having the driving force of rearomatization, the subsequent 1,3-borotropic shift was very slow even at elevated temperature, and considerable protodeboronation occurred. DFT calculations showed that rearomatization lowered the barrier for the 1,3-borotropic shift from 37 to 25 kcal/mol (see SI for details). We therefore investigated the use of Lewis acids to promote the 1,3-borotropic shift by coordinating to oxygen, hence reducing the p_O – p_B π -donation.¹¹ The dramatic effect π -donation of the ligand to boron has on the rate of the 1,3-borotropic shift is shown by the fact that allyl boranes¹² undergo 1,3-borotropic shifts much faster than pinacol boronic esters (-78°C vs $>120^\circ\text{C}$),¹⁰ whereas diamino boranes¹³ require very high temper-

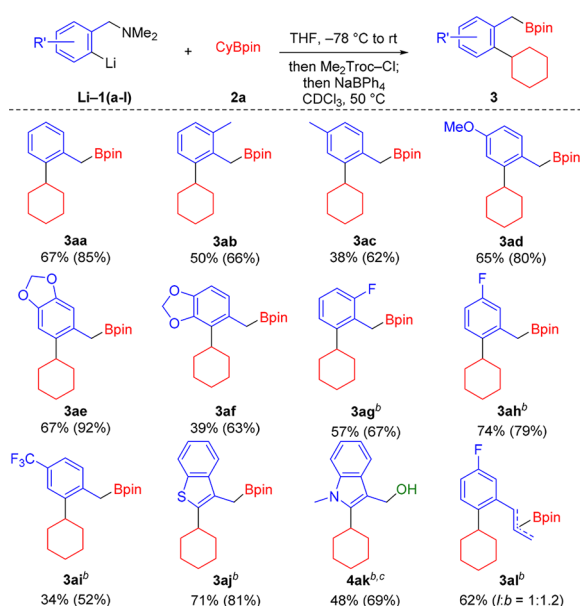
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atures (>200 °C).¹² Unfortunately, most of the Lewis acids tested led to decomposition of the dearomatized intermediate (see SI for details). Interestingly, the addition of 12-crown-4 prevented the 1,3-borotropic shift, indicating that the LiCl generated during the reaction was catalyzing the rearrangement. To increase its potency, we performed an *in situ* salt metathesis with NaBPh₄ and a solvent exchange to noncoordinating chloroform to give “naked” LiBPh₄,¹⁴ which then efficiently catalyzed the reaction affording the benzylic boronate product **3aa** in 85% NMR and 67% isolated yield.

Following this protocol, a series of *ortho*-lithiated benzylamines **Li-1** (generated either by Br/Li exchange or directed lithiation, see SI for details) was tested with CyBpin (**2a**) to assess the scope of the aromatic component that can be employed in this transformation (Scheme 2). A broad range of

Scheme 2. Scope of Lithiated Benzylamines^a



^aReactions were carried out with 0.50 mmol of boronic ester, 1.05 equiv of Ar-Li, 1.10 equiv of **Me₂Troc-Cl** and 1.00 equiv of NaBPh₄. Yields recorded are those of isolated material (NMR yields in brackets). ^b1,3-Borotropic shift conducted at 65 °C. ^cProduct isolated after oxidation with sodium perborate (see SI for details).

electron-rich (**3ab–3af**) and electron-poor (**3ag–3ai**) aromatics can be used in this coupling reaction, as well as heteroaromatic compounds exemplified by **3aj** and **4ak**. Finally, an allylic amine was also tested to afford allylic boronic ester **3al** (*l:b* = 1:1.2). Products **3aa–3al** were obtained in 52–92% NMR yield, with slightly lower isolated yields due to the moderate stability of primary benzylic boronic esters on silica gel. Furthermore, the reaction was readily scalable, and **3aa** was obtained in 64% isolated yield on a 10 mmol scale employing a catalytic amount of NaBPh₄ (10 mol %).

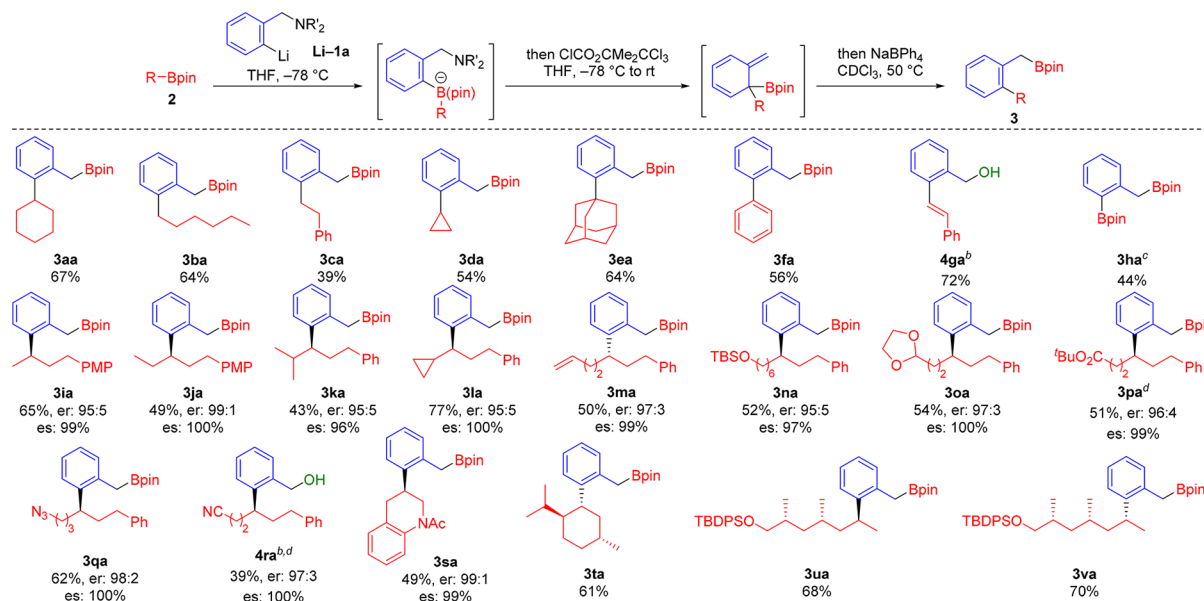
The scope of the boronic ester was also explored (Scheme 3) and included primary, secondary, aryl, and alkenyl boronic esters (**3aa–3ga**). Furthermore, the tertiary boronic ester **AdBpin** (**2e**) and even B₂pin₂ (**2h**) afforded the corresponding products in 64% and 44% isolated yield, respectively. Essentially perfect enantiospecificity was observed for enantio- and diastereo-enriched boronic esters (**2i–2v**) to afford the corresponding products **3ia–3va** in high enantiomeric purity (*er* = 95:5 to 99:1, *dr* >20:1). Importantly, a broad range of functional groups were

well tolerated, highlighting synthetic utility of this dearomatizing 1,2-metalate rearrangement/rearomatizing 1,3-borotropic shift process.

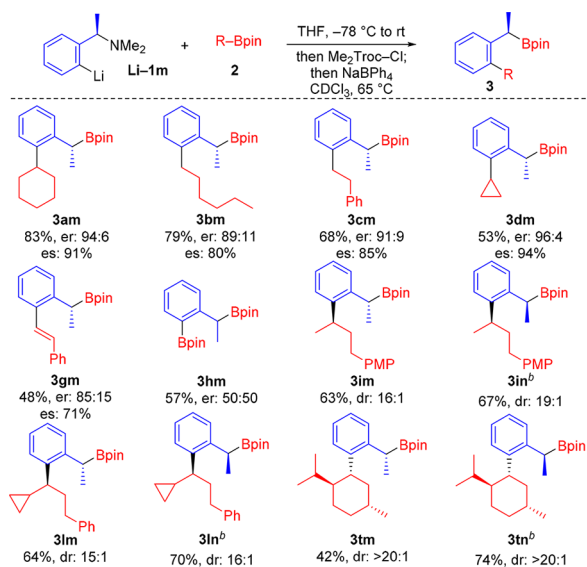
We also investigated the use of readily available enantioenriched α -substituted benzylamines (Scheme 4). Following the standard procedure, reaction of **2a** with *ortho*-lithiated benzylamine **Li-1m** yielded the corresponding secondary boronic ester **3am** with 94:6 *er* and formal retention of configuration, indicating a high preference for the *anti*-S_N2' elimination pathway. Similarly, the reaction with **2d** afforded **3dm** with 96:4 *er*, whereas primary boronic esters **2b** and **2c** gave slightly reduced enantiospecificity (89:11 and 91:9 *er*, respectively). Importantly, the combination of enantioenriched boronic esters with either enantiomer of the *ortho*-lithiated α -methylbenzylamine afforded the corresponding, diastereomeric products **3im–3tn** with excellent diastereomeric ratios, indicating that the reaction does not suffer from significant matched/mismatched effects.

To determine the origin of both the sense and the level of stereospecificity, we performed further experimental and computational investigation. For the transformation of secondary boronic ester **2i** (95:5 *er*) with the *R* enantiomer of the *ortho*-lithiated benzyl amine **Li-1m** (99:1 *er*) to give boronic ester product **3im**, NMR analysis of the dearomatized intermediate showed a *dr* of 92:8, suggesting that the acylation-triggered 1,2-metalate rearrangement/fragmentation proceeded with 94% stereospecificity (Scheme 5), similar to that of secondary boronic esters **2a** and **2d**. Upon 1,3-borotropic shift, which was initiated through salt metathesis/solvent exchange, the benzylic boronic ester product was isolated in similar levels of diastereoselectivity,¹⁵ pointing toward a highly stereospecific 1,3-borotropic shift, as expected.

DFT calculations (B3LYP/6-31G*) revealed that the less-than-perfect level of stereospecificity of the acylation-triggered 1,2-metalate rearrangement/fragmentation step was locked in at the acylation event (see SI for details). Specifically, both the *syn* and *anti* conformers of a zwitterionic *N*-acylated amino boronate of the type under investigation undergo C–N bond cleavage with a very low-barrier (<2 kcal/mol), significantly more facile than interconversion of the conformers through bond rotation (>17 kcal/mol; Figure 1). As expected, for all low-energy conformers, the benzylic hydrogen atom lies approximately in the plane of the aromatic ring pointing toward the boronate moiety. The resulting zwitterionic boronate carbenium species then undergoes a similarly facile 1,2-metalate rearrangement (~1.4 kcal/mol). A low-energy transition state for a more concerted 1,2-metalate rearrangement/fragmentation for either the *syn* or the *anti* conformer could not be identified, presumably owing to steric hindrance. These results show that both *syn* and *anti* conformers of the putative intermediate cannot interconvert and lead to stereoisomeric products with equal facility. Therefore, the higher levels of enantiospecificity for the transformation of secondary boronic esters (>90%) relative to that of primary boronic esters (~80%; see Scheme 4) has its origins in the former engendering a more selective *N*-acylation of the *anti* conformer of the amino boronate intermediate relative to the corresponding *syn* conformer. The surprisingly precarious origin of stereospecificity, as suggested by computation, was borne out experimentally where simply replacing the dimethyl amino group with a diethyl amino group for the transformation of **CyBpin** led to a switch in the sense of stereospecificity (94:6 versus 25:75 *er*; see SI for details).

Scheme 3. Stereospecific Coupling of *ortho*-Lithiated *N,N*-Dialkyl Benzylamine with Boronic Esters^a

^aReactions were carried out with 0.50 mmol of boronic ester, 1.05 equiv of Ar-Li, 1.10 equiv of Me₂Troc-Cl, and 1.00 equiv of NaBPh₄. Yields recorded are those of isolated material; er determined by HPLC analysis. ^bProduct isolated after oxidation (see SI for details). ^c1,3-Borotropic shift conducted at rt. ^dBoronate complex formed at -100 °C.

Scheme 4. *ortho*-Lithiated α -Methylbenzylamines^a

^aReactions were carried out with 0.50 mmol of boronic ester, 1.05 equiv of Ar-Li, 1.10 equiv of Me₂Troc-Cl, and 1.00 equiv of NaBPh₄. Yields recorded are those of isolated material; es determined by HPLC analysis; dr determined by ¹H NMR analysis of purified product. ^bEnantiomeric (S)-2-(1-(dimethylamino)ethyl)phenyl)lithium Li-1n was used instead.

Scheme 5. Mechanistic Analysis with Boronic Ester 2i

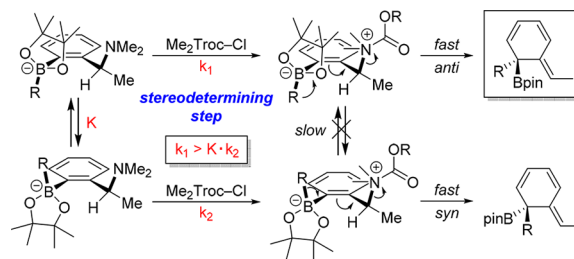
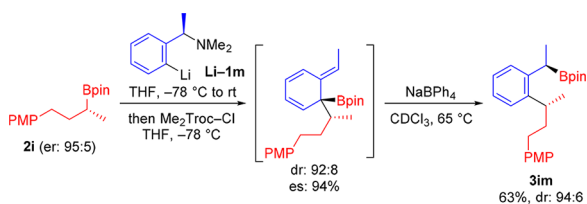
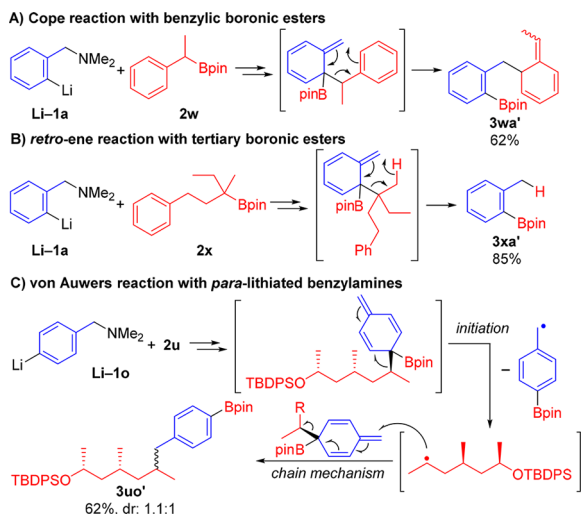


Figure 1. Reaction profile of the acylation-triggered 1,2-metalate rearrangement/fragmentation step.

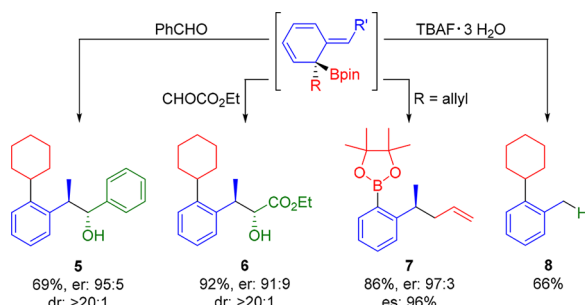
However, not all of the boronic esters tested worked. Notable exceptions included benzylic and tertiary boronic esters (with the exception of AdBpin (2e, *vide supra*)). In both cases, the 1,2-metalate rearrangement occurred, but the dearomatized intermediate did not undergo the 1,3-borotropic shift. In the former case, the intermediate underwent a Cope rearrangement to yield arylboronic ester 3wa' instead (Scheme 6a). In the latter case, a *retro*-ene reaction intervened affording the *ortho*-tolylboronic ester 3xa' (Scheme 6b). This reaction does not occur for AdBpin (2ea, Scheme 3), as an *anti*-Bredt product would arise. Finally, dearomatized intermediates generated from *para*-lithiated benzylamines did not undergo a double 1,3-borotropic shift sequence (Scheme 6c). Instead, a non-stereoselective von Auwers-type reaction¹⁶ afforded arylboronic ester 3uo' with formal inverse 1,4'-benzylidene insertion.

The synthetic utility of the dearomatized intermediate is not restricted to the 1,3-borotropic-shift process (Scheme 7). For example, allylboration of benzaldehyde or ethyl glyoxalate afforded the corresponding alcohols 5 and 6 with excellent diastereo- and enantiocontrol (dr > 20:1, er = 95:5 and 91:9, respectively).¹⁷ Similarly to benzylic boronic esters (Scheme 6a), the intermediate prepared from allylBpin underwent an enantiospecific Cope rearrangement to give 7 with 97:3 er. That the Cope rearrangement is significantly more facile than

Scheme 6. Unsuccessful Substrates



Scheme 7. Synthetic Utility of Intermediate



the 1,3 borotropic shift was confirmed through computation (see SI for details). Finally, treatment of the intermediate with TBAF trihydrate¹⁸ selectively yielded protodeboronation product **8**, an example in which the benzylic amine acted as a traceless directing group.

In conclusion, a new strategy for the stereospecific synthesis of *ortho*-substituted benzylic boronic esters has been developed. The method relies on a 1,2-metalate rearrangement/*anti*- S_N2' reaction followed by a suprafacial 1,3-borotropic shift giving rise to sp^2 – sp^3 cross-coupled products in high enantiopurity in which the boronic ester moiety is retained for further transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b05880.

Detailed experimental procedures and characterization of all products (PDF)

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Notes

The authors declare no competing financial interest.

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